0.5 µl of 2.5 units/µl DNA polymerase ("Cloned Pfu polymerase," product of Stratagene), 10 µl of 25 mM dNTP mix, and further admixed with the oligonucleotide shown by 5'-ACNCCNGTNWSNCA-3' (SEQ ID NO:52) as a sense primer, chemically synthesized on the basis of the amino acid sequence of SEQ ID NO:3, and the oligonucleotide shown by 5'-TGNGCNARNACNACRTG-3' (SEQ ID NO:53) as an antisense primer, chemically synthesized on the basis of the amino acid sequence of SEQ ID NO:8, both in a volume of 10 µM, and the total volume was adjusted to 100 µl with sterilized-distilled water. This mixture was incubated under 40 cycles of the sequential conditions at 94°C, 40°C, and 72°C for 1 minute each to effect PCT.--

Please replace the paragraph beginning at page 21, line 7, with the following rewritten paragraph:

--A portion of the PCR product was collected and then electrophoresed on 1%(w/v) agarose gel to separate DNA fragments, and the DNA fragments were transferred to a nylon membrane and fixed thereon with 0.4 N sodium hydroxide. The membrane was washed with 2 x SSC, dried in air, immersed in prehybridization solution containing 6 x SSPE, 5 x Denhardt's solution, 0.5%(w/v) SDS, and 100 µg/ml denatured salmon sperm DNA, and incubated at 65°C for hours. A probe was prepared by chemical synthesis of the oligonucleotide shown by 5'-GGRCANGGRTCYTT-3' (SEQ ID NO:54), based on the amino acid sequence shown in SEW ID NO:3, and isotope-labeling thereof with [γ-^{32}P]ATP by T4 polynucleotide kinase. To the pre-

hybridization solution in which the above nylon membrane had been immersed, 1 pmol of the probe was added, and the nylon membrane was incubated at 40°C for another 20 hours to effect hybridization. The nylon membrane was washed with 6 x SSC and subjected to autoradiography in a usual manner. A specific hybridization signal by the nylon membrane was incubated at 40°C for another 20 hours to effect hybridization. The nylon membrane was washed with 6 x SSC and subjected to autoradiography in a usual manner. A specific hybridization signal by the probe was observed. This showed that the above PCR product contained the objective DNA fragment.--

Please replace the paragraph bridging pages 21 and 22 with the following rewritten paragraph:

--To the remaining part of the above PCR product, 1 ng of a plasmid vector ("pCR-Script Cam SK(+)," produced by Stratagene) was added, and the DNA fragment of the PCR product was inserted into the vector with a DNA ligation kit ("DNA Ligation Kit, Version 2," produced by Takara Shuzo Co., Ltd.). With a portion of the reaction mixture collected, an *Escherichia coli* strain ("XL1-Blue' MRF' Kan," produced by Stratagene) was transformed. The transformant was inoculated in LB medium (pH 7.5) containing 30 μg/ml chloramphenicol and cultured at 37°C for 18 hours. The cells were collected from the culture. The plasmid DNA was collected from the cells in a usual manner, and analyzed by dideoxy method. This plasmid DNA comprised the nucleotide sequence shown in SEQ ID NO:34 as the

sequence of the DNA fragment produced by PCR. The amino acid sequence encoded by this nucleotide sequence, aligned therewith, were compared with the partial amino acid sequences determined in Examples 1-2 to 1-3, shown in SEQ ID NOs:3 to 23. These partial amino acid sequences were completely or partly included by the amino acid sequence (SEQ ID NO:42) aligned in SEQ ID NO:34. This suggested that the nucleotide sequence shown in SEQ ID NO:34 encodes at least a part of the IL-18-binding protein of human origin.--

Please replace the paragraph beginning at the bottom of page 22, with the following rewritten paragraph:

--Ten nanograms of human liver poly(A)$^+$ RNA (product of Clontech) was subjected to 5'RACE, a modified method of PCR, with a commercially available 5'RACE kit ("5'RACE System, Version 2.0," product of GIBCO BRL). First, reverse transcriptase reaction was effected on the above RNA with the oligonucleotide shown by 5'GGTCACTTCCAATGCTGGACA-3' (SEQ ID NO:55) as a primer, chemically synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:34, and to the 5'-terminal of the first strand cDNA synthesized thereby, C-tail was added by the action of terminal deoxynucleotidyl transferase. Then, PCR was effected on this first strand cDNA with the oligonucleotide shown by 5'-GGCCACGCGTCGACTAGTACGGGIIGGGIIGGGIIG-3' (SEQ ID NO:56) as a sense primer, included by the above kit, and the oligonucleotide shown by 5'-GTCCTTTGTGCTTCTAACTGA-3' (SEQ ID

NO:57) as an antisense primer, chemically synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:34. A portion of the produce of this 5'RACE was collected, and electrophoresed in a usual manner on 1%(w/v) agarose. Specific amplification of a DNA fragment was observed. This DNA fragment was sequenced similarly as in Example 2-1(a). This fragment comprised the nucleotide sequence shown in SEQ ID NO:35. The sequence from the 160th to 216th nucleotides of this sequence completely matched with the sequence from the 1st to 57th nucleotides of the nucleotide sequence shown in SEQ ID NO:34, determined in Example 2-1(a). This suggested that the nucleotide sequence shown in SEQ ID NO:35 overlaps with the nucleotide shown in SEQ ID NO:34, encoding at least a part of the IL-18-binding protein (SEQ ID NO:43) of human origin, and comprises the 5'-upsteam region of SEQ ID NO:34.--

Please replace the paragraph beginning at page 24, with the following rewritten paragraph:

--Ten nanograms of human liver poly(A)$^+$ RNA was subjected to 3'RACE, a modified method of PCR, in accordance with "PCR Jikken Manual (Manual for PCR Experiments)," transplanted by Takashi Saito, published by HBJ Press (1991), 25-33. First, reverse transcriptase reaction was effected on the above RNA with the oligonucleotide shown by 5'-GACTCGAGTCGACATCGA$(T)_{17}$-3' (SEQ ID NO:58) as a primer. Then, PCR was effected on the first strand cDNA synthesized thereby with the oligonucleotide shown by 5'-TTCTCCTGTGTGCTCGTGGA-3'

(SEQ ID NO:59) as a sense primer, chemically synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:34, determined in Example 2-1(a), and the oligonucleotide shown by 5'-GACTCGAGTCGACATCG-3' (SEQ ID NO:60) as an antisense primer. A portion of the product of this 3'RACE was collected and electrophoresed in a usual manner on 1%(w/v) agarose. Specific amplification of a DNA fragment was observed. This DNA fragment was sequenced similarly as in Example 2-1(a). This fragment comprised the nucleotide sequence shown in SEQ ID NO:36. The sequence from the 1st to 60th nucleotides of this sequence completely matched with the sequence from the 352nd to 411st nucleotides of the nucleotide sequence shown in SEQ ID NO:34, determined in Example 2-1(a). This suggested that the nucleotide sequence shown in SEQ ID NO:36 (SEQ ID NO:44) overlaps with the nucleotide sequence shown in SEQ ID NO:34, encoding at least a part of the IL-18-binding protein of human origin, and comprises the 3'-downstream region of SEQ ID NO:34.--

Please replace the two paragraphs beginning at page 25, line 11, and ending at page 26, line 20, with the following rewritten paragraphs:

--In accordance with the method in Example 2-1(a), reverse transcriptase reaction was effected on human liver poly(A)$^+$ RNA, and then PCR was effected similarly as in Example 2-1(a) except for using as a sense primer the oligonucleotide shown by 5'-TGTGTGACTGGAGAAGAGGAC-3' (SEQ ID NO:50), chemically

synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:37, and as an antisense primer the oligonucleotide shown by 5'-TACAGGCAGTCAGGGACTGTTCACTCCAG-3' (SEQ ID NO:51), chemically synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:37. A portion of the PCR product was collected, and electrophoresed in a usual manner on 1%(w/v) agarose gel. Specific amplification of a DNA fragment was observed. This DNA fragment was sequenced similarly as in Example 2-1(a). This fragment comprised the nucleotide sequence shown in SEQ ID NO:37. This supported that the nucleotide sequences shown in SEQ ID NOs:34 to 36, determined in Examples 2-1(a) to 2-1(c), are partial sequences of the contiguous nucleotide sequence shown in SEQ ID NO:37.

cont a4

The amino acid sequence (SEQ ID NO:45) encoded by the nucleotide sequence shown in SEQ ID NO:37, aligned therewith, are compared with the partial amino acid sequences shown in SEQ ID NOs:4 to 23, determined in Example 1-3. These partial sequences were all included by the amino acid sequence aligned in SEQ ID NO:37 in the region from the 1st to 164th amino acids. In addition, the N-terminal amino acid sequence determined in Example 1-2, shown in SEQ ID NO:3, well matched with the amino acid sequence aligned in SEQ ID NO:37 in the region from the 1st to 22nd amino acids. These facts suggested that the nucleotide sequence shown in SEQ ID NO:37 can encode the IL-18-binding protein of human origin by the region from the 160th to 651st nucleotides and that this IL-18-binding protein may has, as its whole sequence, the sequence from the

1st to 164th amino acids of the amino acid sequence aligned with this nucleotide sequence. Thus suggested amino acid sequence of the IL-18-binding protein of human origin and the nucleotide sequence encoding this are shown in SEQ ID NOs:1 and 32 separately.--

Please replace the paragraph at the bottom of page 26, with the following rewritten paragraph:

--A DNA capable of encoding the IL-18-binding protein of human origin, obtained by the method in Example 2-1(d), was placed in a 0.5-ml reaction tube in an amount of 1 ng, and to this tube, 10 µl of 10 x PCR buffer, 1 µl of 25 mM dNTP mix, and 2.5 units/µl DNA polymerase ("Cloned Pfu polymerase," produced by Stratagene) were added. Appropriate amounts of the oligonucleotide shown by 5'-CTCGAGGCCACCATGACCATGAGACACAAC-3' (SEQ ID NO:61) as a sense primer, chemically synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:32, and the oligonucleotide shown by 5'-GCGGCCGCTCATTAGTGATGGTGATGGTGATGACCCTGCTGCTGTGGACT-3' (SEQ ID NO:62) as an antisense primer, chemically synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:32, were further added to the above tube, and the total volume was adjusted to 100 µl with sterilized-distilled water. PCR was effected by incubating this mixture under 3 cycles of the sequential conditions at 94°C for I minute, at 42°C for 2 minutes, and at 72°C for 3 minutes and then 35 cycles of the

sequential conditions at 94°C for 1 minute, at 60°C for 2 minutes, and 72°C for 3 minutes. The PCR product was analyzed and manipulated similarly as in Example 2-1(a); the PCR product was confirmed to contain the objective DNA fragment, and a plasmid vector inserted with this DNA fragment was obtained. This plasmid DNA comprised the nucleotide sequence shown in SEQ ID NO:32, confirmed by sequencing similarly as in Example 2-1(a).--

Please replace the paragraph beginning at page 33, line 14, with the following rewritten paragraph:

--Reverse transcriptase reaction was effected similarly as *in* Example 2-1(a) on this total RNA, and PCR was effected on this reaction product containing first strand cDNA similarly as in Example 2-1(a) except for using as a sense primer the oligonucleotide shown by 5'-GCNGTNCCNACNAA-3' (SEQ ID NO:63), chemically synthesized on the basis of the amino acid sequence shown in SEQ ID NO: 27, and as an antisense primer the oligonucleotide shown by 5'-GTYTTNARNCCRTC-3' (SEQ ID NO:64), chemically synthesized on the basis of the amino acid sequence shown in SEQ ID NO:30. A probe was prepared from the oligonucleotide shown by 5'-SWNCTRTGNCCYTCYTT-3' (SEQ ID NO:65), chemically synthesized on the basis of the amino acid sequence shown in SEQ ID NO:24. By using this probe and by the procedure according to Example 2, the above PCR product was confirmed to contain the objective DNA fragment. This DNA fragment was sequenced similarly as in Example 2-1(a). This

fragment comprised the nucleotide sequence shown in SEQ ID NO:38. The amino acid sequence (SEQ ID NO:46) aligned in SEQ ID NO:38 was compared with the partial amino acid sequences shown in SEQ ID NOs:24 to 31, determined in Example 3-2. These partial amino acid sequences were completely or partly included by the amino acid sequence aligned in SEQ ID NO:38. This suggested that the nucleotide sequence shown in SEQ ID NO:38 encodes at least a part of the IL-18-binding protein of mouse origin.--

Please replace the paragraph beginning on page 34, line 14 with the following rewritten paragraph:

--Total RNA was collected similarly as in Example 4-1(a) from female CD-1 mice treated with the dead cells of *Corynebacterium parvum* and lipopolysaccharide, and 1 μg of the total RNA was subjected to 5'RACE, a modified method of PCR, with a commercially available 5'RACE kit ("5'RACE System, Version 2.0," product of GIBCO BRL). First, reverse transcriptase reaction was effected on the above total RNA with the oligonucleotide shown by 5'-TGCAGGCAGTACAGGACAAGG-3' (SEQ ID NO:66) as a primer, chemically synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:38, and to the 5'-terminal of the first strand cDNA synthesized thereby, C-tail was added by the action of terminal deoxynucleotidyl transferase. Then, PCR was effected on this first strand cDNA with the oligonucleotide shown by 5'-GGCCACGCGTCGACTAGTACGGGIIGGGIIGGGIIG-3' (SEQ ID NO:56) as a sense primer, included by the kit, and the oligonucleotide

shown by 5'-GTGCTGGGTACTGCTTAGTTG-3' (SEQ ID NO:67) as an antisense primer. A portion of this 5'RACE product was collected, and electrophoresed in a usual manner on 1%(w/v) agarose gel. Specific amplification of a DNA fragment was observed. This DNA fragment was sequenced similarly as in Example 2-1(a). This fragment comprised the nucleotide sequence shown in SEQ ID NO:39. The sequence from the 307th to 336th nucleotides of this sequence completely matched with the sequence of the 1st to 30th nucleotides of the sequence shown in SEQ ID NO:38, determined in Example 4-1(a). This suggested that the nucleotide sequence shown in SEQ ID NO:39 overlaps with the nucleotide sequence shown in SEQ ID NO:38, encoding at least a part of the IL-18-binding protein (SEQ ID NO:47) of mouse origin, and comprises the 5'-upstream region of SEQ ID NO:38.--

cont a10

Please replace the paragraph beginning at page 35, line 19, with the following rewritten paragraph:

--Total RNA was collected similarly as in Example 4-1(a) from female CD-1 mice treated with the dead cells of *Corynebacterium parvum* and lipopolysaccharide, and 1 μg of the total RNA was subjected to 3'RACE, a modified method of PCR, in accordance with the methods described in "PCR *Jjkkeri* Manual (Manual for PCR Experiments)," translated by Takashi Saito, published by HBJ Press (1991), pp.25-33. First, reverse transcriptase reaction was effected on the above total RNA with the oligonucleotide shown by 5'-GACTCGAGTCGACATCGA$(T)_{17}$-3' (SEQ ID NO:58) as a primer. Then,

a11

PCR was effected on the first strand cDNA synthesized thereby with the oligonucleotide shown by 5'-GATCCTGGACAAGTGGCC-3' (SEQ ID NO:68) as a sense primer, chemically synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:38, determined in Example 4-1(a), and the oligonucleotide shown by 5'-GACTCGAGTCGACATCG-3' (SEQ ID NO:60) as an antisense primer. A portion of this 3'RACE product was collected, and electrophoresed in a usual manner on 1%(w/v) agarose gel. Specific amplification of a DNA fragment was observed. This DNA fragment was sequenced similarly as in Example 2-1(a). This fragment comprised the nucleotide sequence shown in SEQ ID NO:40. The sequence from the 1st to 63rd nucleotides of this sequence completely matched with the sequence of the 289th to 351st nucleotides of the sequence shown in SEQ ID NO:38, determined in Example 4-1(a). This suggested that the nucleotide sequence shown in SEQ ID NO:40 overlaps with the nucleotide sequence shown in SEQ ID NO:38, encoding at least a part of the IL-18-binding protein (SEQ ID NO:48) of mouse origin, and comprises the 3'-downstream region of SEQ ID NO:38.--

Please replace the paragraph beginning at page 37, line 3 with the following rewritten paragraph:

--Total RNA was collected similarly as in Example 4-1(a) from female CD-1 mice treated with the dead cells of *Corynebacterium parvum* and lipopolysaccharide. After reverse transcriptase reaction was effected on this total RNA, PCR was effected similarly as in Example 4-1(c) except for using the

oligonucleotide shown by 5'-CTGAGCCTTAGAGCTCCAAG-3' (SEQ ID NO:69) as a sense primer and the oligonucleotide shown by 5'-GTGAAGCTTGAGTTTGAGGTTC-3' (SEQ ID NO:70) as an antisense primer, both chemically synthesized on the basis of the nucleotide sequence shown in SEQ ID NO:41. A portion of this PCR product was collected, and electrophoresed in a usual manner on 1%(w/v) agarose gel. Specific amplification of a DNA fragment was observed. This DNA fragment was sequenced similarly as in Example 2-1(a). This fragment comprised the nucleotide sequence shown in SEQ ID NO:41.--

Please replace the paragraph bridging pages 37 and 38 with the following rewritten paragraph:

--The amino acid sequence (SEQ ID NO:49) encoded by the nucleotide sequence shown in SEQ ID NO:41, aligned therewith, are compared with the partial amino acid sequences shown in SEQ ID NOs:24 to 31, determined in Example 3-2. These partial sequences were all included by the amino acid sequence aligned in SEQ ID NO:41 in the region from the 1st to 165th amino acids. In addition, the amino acid sequence of the IL-18-binding protein of human origin shown in SEQ ID NO:1 exhibited about 61% homology with the amino acid sequence aligned in SEQ ID NO:41 in the region from the 1st to 165th amino acids. These facts suggested that the nucleotide sequence shown in SEQ ID NO:41 can encode the IL-18-binding protein of mouse origin by the region from the 235th to 729th nucleotides and that this IL-18-binding protein may have, as its whole sequence, the sequence from the first to 165th amino

acids of the amino acid sequence aligned with this nucleotide sequence. The amino acid sequence thus suggested as that of the IL-18-binding protein of mouse origin and the nucleotide sequence encoding this are shown in SEQ ID NOs:2 and 33 separately.--

Please replace the paragraph beginning at page 38, line 18 with the following rewritten paragraph:

--A DNA capable of encoding the IL-18-binding protein of mouse origin, obtained by the method in Example 4-1(d), was placed in a 0.5-ml reaction tube in an amount of 1 ng, and this DNA was treated similarly as in Example 2-2(a) except for using the oligonucleotide shown by 5'-CTCGACGCCACCATGACCATGAGACACTGC-3' (SEQ ID NO:71) as a sense primer and the oligonucleotide shown by 5'-GCGGCCGCTCATTAGTGATGGTGATGGTGATGTGCAACCCCTGGGCCTGC-3' (SEQ ID NO:72), as an antisense primer, both on the basis of the nucleotide sequence shown in SEQ ID NO:33. Similarly as in Example 4-1(a), the PCR product was confirmed to contain the objective DNA fragment, and a plasmid vector inserted with this DNA fragment was obtained. This plasmid DNA was sequenced similarly as in Example 2-1(a). The plasmid DNA comprised the nucleotide sequence shown in SEQ ID NO:33.--

REMARKS

Applicants have added into the present specification a new paper copy Sequence Listing section according to 37